Systemic Anti Cancer Treatment Protocol

Encorafenib and Cetuximab Metastatic Colorectal Cancer

PROTOCOL REF: MPHAENCEGA
(Version No: 1.1)

Approved for use as an interim measure during COVID-19 pandemic.

Approved for use in:

Metastatic colorectal adenocarcinoma with RAS wild type and BRAF V600E mutation where the following conditions are met:

- ECOG performance status (PS) of 0 – 1
- Failed **one or two** lines of previous therapy. Previous treatment with EGFR (cetuximab, panitumumab), BRAF or MEK inhibitors not permitted. Progression through adjuvant chemotherapy or within 6 months of completing adjuvant chemotherapy qualifies as one line of treatment for metastatic disease.
- No active brain metastases or leptomeningeal metastases.

****************************Blueteq registration required****************************

Note: risk of haemorrhage, cardiovascular, dermatological and ocular toxicities should be taken into consideration when reviewing co-morbidities.

Baseline liver function tests must be reviewed prior to completing consent process (Please refer to 'Dosing in renal and hepatic impairment section'). As per trial, adequate hepatic function was characterised by the following:

- **Serum total bilirubin (BIL) ≤ 1.5 × ULN P (Note: total BIL > 1.5 × ULN allowed if their indirect BIL ≤ 1.5 × ULN**
- **Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 × ULN, or ≤ 5 × ULN in presence of liver metastases.**

Dosage:

Drug	Dosage	Route	Frequency
Encorafenib	300mg once daily	Oral	Continuous Supplied every 28 days
Cetuximab	500mg/m^2	IV	Every 14 days

28 day cycle to continue until disease progression or unacceptable toxicity

Administration

Counselling Points:

Encorafenib is available as 50mg and 75mg capsules.

Patients should be encouraged to take encorafenib with approximately 200 mL of water with or without food. The capsules should be swallowed whole, not crushed or chewed.

Ensure appropriate contraception is discussed.

Patient should avoid any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos within 7 days prior to start of treatment and until treatment discontinuation, as these have been shown to inhibit CYP3A4 activity.

Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect their ability to drive or operate machinery. Refer to 'Main Toxicities' section for detailed information on precautions/warning signs.

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) (including kerathoacanthoma) and new primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib. **Patients should be instructed to immediately inform their physicians if new skin lesions develop.**

Emetogenic risk:

Moderate

Supportive treatments:

Pliazon plus cream for cetuximab rash

Cyclizine 50mg up to three times a day when required

Loperamide 4mg immediately after first episode of loose stool then 2mg to be taken after each subsequent episode to a maximum of 8 tablets in 24 hours.

Extravasation risk:

Cetuximab in a monoclonal antibody- Neutral

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Encorafenib	GFR 30-90 ml/min- no dose adjustment required USE WITH CAUTION AS NOT STUDIED IN THESE PATIENT GROUPS: GFR < 30 ml/min or Haemodialysis (HDx) **without hepatic impairment:** no need for dose adjustment is expected
	Cetuximab	All grades of renal impairment or patients on HDx- no need for dose adjustment is expected.

Hepatic	Encorafenib	Mild to severe hepatic impairment may cause increased encorafenib exposure (mild up to 25% higher). <u>Mild hepatic impairment (Child-Pugh Class A)</u> - use with caution at a dose of 300 mg once daily. <u>Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment</u> - Not studied in this patient group. **Not recommended.**

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin	> 35	28–35	< 28

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>(g/L)</td><td></td><td></td><td></td></tr>
<tr><td>Prothrombin time, prolongation (s)
Or
INR</td><td>< 4

< 1.7</td><td>4–6

1.7-2.3</td><td>> 6

>2.3</td></tr>
<tr><td>Ascites</td><td>None</td><td>Mild to Moderate (diuretic responsive)</td><td>Severe (diuretic refractory)</td></tr>
<tr><td>Hepatic encephalopathy</td><td>None</td><td>Grade I–II (or suppressed with medication)</td><td>Grade III–IV (or refractory to medication)</td></tr>
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INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.
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<tr><td></td><td>Cetuximab</td><td>All grades of hepatic impairment: no need for dose adjustment is expected</td></tr>
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Interactions:

The number of affected medicinal products expected to interact with encorafenib are extensive; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to CYP3A inducers/inhibitors/substrates and UGT1A1 substrates.

Encorafenib potentially inhibits a number of transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OATP1B1, OATP1B3, OCT1 (such as atorvastatin, bosentan) or substrates of BCRP (such as methotrexate, rosuvastatin) or substrates of P-gp (e.g. posaconazole) may have increased exposure and should be therefore co-administered with caution.

Refer to SmPC for each agent for full details on interactions. For any interaction queries please contact Cytopharmacy.

Treatment schedule:

Day	Drug	Dosage	Route	Administration Directions
1	**Dexamethasone**	8mg	PO	30 minutes prior to treatment
1	**Chlorphenamine**	10mg	IV	Bolus injection 30 minutes prior to treatment
1	**Cetuximab**	500mg/m^2	IV	Infuse first dose over 2 hours then reduce to 1 hour as tolerated
1 to 28	**Encorafenib**	300mg	PO	daily
15	**Dexamethasone**	8mg	PO	30 minutes prior to treatment
15	**Chlorphenamine**	10mg	IV	Bolus injection 30 minutes prior to treatment
15	**Cetuximab**	500mg/m^2	IV	Infuse first dose over 2 hours then reduce to 1 hour as tolerated

Allergic reactions during cetuximab infusion can occur.

Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main Toxicities:

The most common ADRs (>25%) reported in this population were: fatigue, nausea, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/musculoskeletal pain, decreased appetite, rash and vomiting.

	Cetuximab	Encorafenib
Dermatological	Skin reactions are very common and treatment interruption or discontinuation may be required. Prophylactic use of oral tetracyclines (6 - 8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered. If a patient experiences an intolerable or severe skin reaction (≥ grade 3) cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2.	**New primary malignancies, cutaneous and non-cutaneous, have been observed. Dermatological evaluations should be performed prior to initiation of treatment. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop.** Cutaneous toxicities including rash, acneiform dermatitis, palmar-plantar erytrodysesthesia (hand-foot skin reaction or HFSR), hyperproliferative skin diseases
Ocular	Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.	Uveitis including iritis and iridocyclitis can occur. Patients should be assessed at each visit for symptoms of new or worsening visual disturbance, including; diminished central vision, blurred vision or loss of vision. If any of these symptoms are identified, a prompt ophthalmologic examination is recommended. For grading and dose modifications refer to

		'**Dose Modifications and Toxicity Management'** section**.**
Hypersensitivity reactions including anaphylaxis	Mild or moderate infusion-related reactions are very common: comprising symptoms such as fever, chills, dizziness or dyspnoea that predominately occur when patients receive their first cetuximab infusion. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions. Close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.	
Electrolyte disturbances	Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcaemia may be increased. **Serum electrolytes abnormalities, including low magnesium and potassium need to be corrected to reduce risk of QT prolongation.**	

Cardiovascular		QT Prolongation has been observed in patients treated with BRAF-inhibitors. Recommended that **serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled** (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment. For grading and dose modifications refer to '**Dose Modifications and Toxicity Management'** section**.**
Haemorrhage		Haemorrhagic events were observed in 21% of patients treated with encorafenib. **Monitor haemoglobin and for epistaxis and blood in stool or urine.**

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1d15	Cycle 2	Cycle 2d15	Ongoing
Clinical Assessment	X			X	X	Alternate cycles
SACT Assessment (to include PS and **toxicities***)	X	X	X	X	X	Every cycle
FBC	X	X		X		Every cycle
U&E & LFT **(ALT,AST and Bilirubin) Including Magnesium**	X	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	Day 1 of every cycle
Ophthalmic exam*	X					As clinically indicated
Dermatological Evaluation*	X					Every 2 months while on therapy and for up to 6 months following treatment discontinuation.
CT scan	X					12 weekly or as clinically indicated
Informed Consent	X					
Blood pressure measurement	X					Repeat if clinically indicated
Respiratory rate						If clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
ECG**	X			X		Every 12 weeks or more frequently as clinically indicated
Height	X					

*** If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. Any new skin lesions should be reviewed by medical team, with referral to specialist teams as soon as possible. Monitor for any bleeding episodes (epistaxis and blood in stool or urine).**

****ECGs to be requested and reviewed by clinical teams. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors (refer to relevant sections in 'Main Toxicities' and 'Dose Modifications and Toxicity Management Section').**

Dose Modifications and Toxicity Management:

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib. See dose recommendations tables below.

If encorafenib is permanently discontinued, cetuximab should be discontinued and vice versa.

For new primary cutaneous malignancies: No dose modifications are required for encorafenib. Refer to 'Main Toxicities' section for detailed information on precautions/warning signs.

For new primary non-cutaneous RAS mutation-positive malignancies: it should be considered to discontinue encorafenib permanently.

Dose level	Encorafenib	Cetuximab
1st dose reduction	225mg once daily	400mg/m^2
2nd dose reduction	150mg once daily	300mg/m^2

Haematological toxicity:

Note that neither cetuximab nor encorafenib are myelosuppressive and no dose reduction is needed for haematological toxicity.

Proceed on cycle 1 day 1 if:-

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L	Haemoglobin ≥ 90 g/L

Delay both treatments 1 week on day 1 for subsequent cycles if:-

ANC ≤ 0.9 x 10^9/L	Platelets < 75 x 10^9/L

Non-haematological toxicity:

Recommended dose modifications for encorafenib when used in combination with cetuximab for SELECTED ADVERSE REACTIONS.

Severity of adverse reaction (CTCAE version 4)	**Encorafenib**
Cutaneous reactions	
• Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
• Grade 3	Encorafenib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence, or resumed at a reduced dose if recurrent Grade 3.
• Grade 4	Encorafenib should be permanently discontinued.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• Grade 2	Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
• Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.
Uveitis including iritis and iridocyclitis	
• Grade 1-3	If Grade 1 or 2 uveitis does not respond to specific (e.g. topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.

• Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.
QTc Prolongation	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld. Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF>500 ms and increased by >60 ms from pre-treatment values	Encorafenib should be permanently discontinued
Liver laboratory abnormalities	
• Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x Upper Limit of Normal (ULN) ≤5x	Encorafenib should be maintained. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resumed at the same dose.
• First occurrence of Grade 3 AST or ALT >5x ULN and Bilirubin >2x ULN	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of Grade 4 AST or ALT >20 ULN	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 AST or ALT > 5x ULN and Bilirubin > 2x ULN	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 AST or ALT > 20 ULN	Encorafenib should be permanently discontinued.

Recommended dose modifications for encorafenib when used in combination with cetuximab for OTHER ADVERSE REACTIONS.

Severity of adverse reaction	Encorafenib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, It should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of any Grade 4 adverse reaction	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib should be permanently discontinued.

References:

Cetuximab 5mg/ml solution for infusion, summary of Product Characteristics, Merck Serono Ltd. Available via https://www.medicines.org.uk/emc https://www.medicines.org.uk/emc (last updated 6th June 2019).

Encorafenib 50 mg hard capsules, summary of Product Characteristics, Pierre Fabre Ltd. Available via https://www.medicines.org.uk/emc https://www.medicines.org.uk/emc (last updated 11th June 2020).

Kopetz et al. (2020) Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. *N Engl J Med*. **382**:876-878

NHS England interim treatment changes during the COVID-19 pandemic (Last updated on 11th September 2020) available via: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.